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Dose escalation with stereotactic body radiotherapy for cervical cancer treatment

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Abstract

Background Dose escalation with brachytherapy after pelvic irradiation is standard for treating cervical cancer. Its application can be impossible for some patients. Dose escalation with SBRT is widely used with high local control and acceptable toxicity rates in different body parts. The study enrolled patients who underwent SBRT treatment for dose escalation in the cervix.

Methods Patients who were pathologically diagnosed and treated with cervical SBRT after definitive CRT were included in the study. A total of 30 Gy in 5 fractions for the high-risk volume was prescribed. The first response evaluation was performed three months after the completion of treatment. Treatment toxicity was documented according to the RTOG-EORTC scale. Oncological outcomes and toxicity were assessed.

Results Between 02.2019 and 05.2023, 40 patients were treated with an SBRT boost after pelvic irradiation. The median follow-up time was 16 months (7–44 months). The median HR CTV was 47 cc (8,3-168,2 cc). There were 39 patients who achieved a complete response and one who achieved a partial response in the third month after treatment. There were two local or two regional recurrences. The 1-year metastasis-free survival was 88%, and the 1-year progression-free survival was 88%. During the follow-up period, one grade 3 gastrointestinal side effect was observed.

Conclusions SBRT which has low toxicity and reasonable locoregional control rates in a short follow-up period, may be an option for dose escalation in brachytherapy-ineligible cervical cancer patients.

Keywords Cervical cancer, SBRT, Stereotactic, Brachytherapy, Chemoradiotherapy

Introduction

Definitive chemoradiation (CRT) is the established treatment modality for locally advanced cervical cancer [1–6]. An increased radiation dose combined with intracavitary brachytherapy is associated with improved disease control and overall survival [3–5]. Despite the absence of randomized trials comparing outcomes between patients who underwent CRT with or without brachytherapy, observational data from national databases have consistently demonstrated improved outcomes with brachytherapy [7, 8].

Despite being the gold standard treatment for cervical cancer, the utilization of brachytherapy has declined in recent years [9]. Several factors may account for this trend, including the invasive nature of brachytherapy necessitating anesthesia, limited accessibility in certain facilities, its user-dependent nature, and the necessity

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for implementation by an experienced team. Moreover, it may not be appropriate for all patients and lesions.

Conversely, emerging technologies such as intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT) have gained momentum. With advancements in radiotherapy planning and image-guided techniques, high rates of local control can be achieved across both intracranial and extracranial sites through the adoption of stereotactic treatments with rapid dose fall-off [11].

The underlying principle of brachytherapy lies in its ability to deliver high-dose radiation to the tumor center while rapidly decreasing peripheral doses, thus minimizing toxicity and maximizing tumor control [12]. Dosimetric evaluations indicate that SBRT dose distributions can replicate the dose fall-off and heterogeneity characteristics of brachytherapy [13, 14]. Therefore, we started with dosimetric analyses and investigated the feasibility of cervix SBRT dosimetry using GEC-ESTRO dose criteria for one fraction as a reference [15]. We found that with an SBRT boost, similar plan quality and dosimetric results can be achieved in cervical cancer patients.

The study enrolled patients who were ineligible or declined brachytherapy treatment for various reasons and who underwent SBRT treatment for dose escalation in the cervix following definitive CRT.

This study presents preliminary oncological outcomes and toxicity profiles associated with SBRT boost following CRT in cervical cancer patients.

Table 1 Target volume definitions

Target volumes	Definition of field borders and target volumes
Pelvic RT	
GTVp	Primary tumor seen on MRI and PET-CT
CTVp	GTVp + Whole cervix, uterus, vagina*, parametrium
GTVn	All visible lymph nodes on MRI and/or PET-CT
CTVn	Common, internal, external iliac, obturator and presacral lymph node regions ± PA
PTVp	CTVp + 5 mm in all directions
PTVn	CTVn + 5 mm in all directions
SBRT boost	
CTVhr	Gross disease on the second MRI and the whole cervix
CTVir	HR CTV plus initial gross tumor volume on first MRI and PET scan
PTVhr	HR CTV + 5 mm in all directions
PTVir	IR CTV + 5 mm in all directions

GTVp: Primary Tumor GTV, CTVp: Primary Tumor CTV, GTVn: Lymph Node GTV, CTVhr: High Risk CTV, CTVir: Intermediate Risk CTV, PA: paraaortic, PTVhr: High Risk PTV, PTVir: Intermediate Risk PTV

*Vaginal target volume defined according to primary tumor extension

Materials and methods

Our institutional ethics committee approved this study (number ASM-EK-21/162). All patients pathologically diagnosed with cervical cancer underwent pelvic examination, contrast-enhanced pelvic magnetic resonance imaging (MRI), and positron emission tomography (PET)-CT for initial staging. All treatment decisions were made by a multidisciplinary tumor board. Informed consent was obtained from all patients before treatment. This study enrolled patients who underwent SBRT treatment for dose escalation and included patients who received definitive CRT for newly diagnosed locally advanced disease, as well as those with metastatic disease who had controlled metastases after systemic treatment and who would receive RT to the primary site and patients with postoperative locoregional recurrence without a history of radiotherapy. All patients were provided with comprehensive information about standard brachytherapy prior to treatment. The data were prospectively recorded and collected from electronic medical records.

Radiotherapy planning

Patients were immobilized with knee and foot supports and scanned in a GE Discovery RT (GE Healthcare, Milwaukee, MI, USA) with a slice thickness of 2.5 mm. CT simulation for the first phase of treatment was performed with an empty rectum and a comfortably full bladder with intravenous contrast. The planning CT, diagnostic pelvic MR, and PET-CT images were transferred and fused within the treatment planning system. The prescribed dose in the first phase was 45 Gy to the whole pelvis, which increased in the radiologically positive lymph nodes with simultaneous integrated boost (SIB) to 62,5 Gy in 25 fractions. If the patients had positive paraaortic lymph nodes (LN), the paraaortic LN region was added to the treatment field.

External Beam Radiotherapy (EBRT) plans were generated with 6 MV photon energy using the Volumetric Modulated Arc Therapy (VMAT) technique on Varian EDGE with HD MLC (version 2.7, Varian Medical Systems, Palo Alto, CA, USA) or the helical IMRT technique on Radixact (version X9, Accuray Inc., Madison, WI, USA) machines.

In the last week of EBRT, between 21 and 23 fractions, a pelvic examination, a new CT simulation (with a 1 mm slice thickness) performed with an empty rectum and a comfortably full bladder, and a contrast-enhanced MR in the treatment position were performed. The second phase was planned according to the response and residual disease discussed with an experienced radiologist. The GEC-ESTRO Study Group criteria were used for target volume delineation (Table 1). A total dose of 30 Gy was prescribed to the high-risk (HR) volume, delivered in five fractions (Fig. 1).

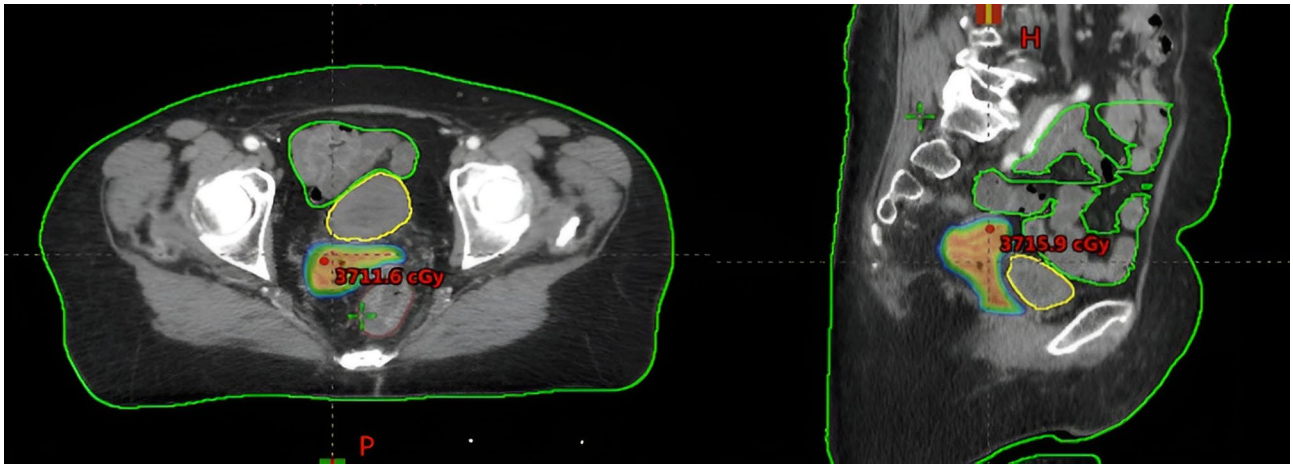

Fig. 1 Representative treatment plan for a patient receiving an SBRT boost. Dose distribution in axial and sagittal views

The Eclipse treatment planning system (version 15.5, Varian Medical Systems, Palo Alto, CA, USA) and VMAT technique with 3 arcs on a 6-MV-FFF linear accelerator Varian EDGE were used for the boost plan.

CT slices, structure sets, and dose distribution data for both EBRT and SBRT treatment plans were exported from the planning system in DICOM format and imported into Velocity software (version 4.1, Varian Medical Systems, Palo Alto, CA, USA). Velocity software is utilized to evaluate delivered doses, compare them with original treatment plans, and account for anatomical and volumetric changes over time, or to analyze cumulative dose information by aggregating data from different treatment periods for the same patient.

To address the different dose and fractionation schemes of EBRT and SBRT, the software computed the equivalent uniform dose in 2 Gy fractions (EQD2) for all plans. The α/β ratio was assumed to be 10 Gy for target volumes and 3 Gy for organs at risk, including the bladder, rectum, sigmoid, vagina, and bowel. Dose summation was performed using the "Multiresolution Elastic B-Spline with Mutual Information Algorithm," which initially applies a semi-rigid alignment to match overall anatomy between the two volumes and then applies additional flexibility to refine the deformation. Deformable dose mapping was carried out using the fusion data from CT scans for cumulative dose assessment. Targets and organs at risk (OARs) were analyzed in the cumulative plan following ASTRO guidelines, with the objective of achieving a D90%> 80 Gy for the high-risk clinical target volume (CTV HR) and a D98%> 60 Gy for the intermediate-risk CTV (CTV IR) [4]. The dose constraints for phase I, phase II, and dose summation criteria are listed in the Supplement. (See additional file)

Treatment delivery

Before each treatment, the bladder volume was checked via ultrasound, and an enema was administered before every SBRT fraction. Cone beam CT images were taken before each fraction and surface guidance with the AlignRT system (Vision RT Ltd, London, UK) was applied for setup and motion tracking. All treatments were performed on consecutive days in the first phase and on alternate days in the second phase.

Side effect and response evaluation

The initial response assessment was conducted three months following the completion of treatment, utilizing a combination of pelvic examination, contrast-enhanced MRI, and PET-CT. Following the initial response evaluation, patients underwent regular follow-up evaluations every three months to assess locoregional control, distant metastasis, and late-onset side effects. The selection of imaging modalities for these evaluations was determined based on the discretion of the attending physician. All recurrences were comprehensively reviewed and evaluated by a multidisciplinary tumor board. In patients with metastatic disease, the development of new metastatic lesions has been defined as distant progression. Patients were evaluated three-monthly for side effects according to the RTOG-EORTC toxicity scale by the same radiation oncologist and recorded electronically [16].

Patient and tumor-related factors, side effects, treatment details and dosimetry, time until first progression after SBRT, type of first progression, and duration of follow-up data were collected.

Statistics

The primary endpoint of this study was to assess toxicity. We aimed to achieve a rate of grade 3 or above adverse effects of less than 10%. The secondary endpoints were local control, regional control, distant control, and

Table 2 Tumor characteristics

Histology	Number (%)
*SCC**	35 (87.5)
Non-SCC	5 (12.5)
FIGO staging (2018)	
IIA2	2 (5)
IIB	5 (12.5)
IIIC1r	25 (62.5)
IIIC2r	5 (12.5)
IVA	3 (7.5)
Lymph node involvement	
None	7 (17.5)
Pelvic	25 (62.5)
Paraaortic	8 (20)
Disease Status	
Primary treatment	34 (85)
Postoperative Recurrence	4 (10)
Metastatic	2 (5)
Reason ineligible for brachytherapy	
Medical	12 (30)
Technical	13 (32.5)
Patient refusal	15 (37.5)

* Squamous cell carcinoma

Table 3 The dosimetric characteristics of the CTVs and critical organs

	EBRT + BOOST (Gy)
HR CTV EQD2 D90%	
Median	86.5
Range	81.6–94.5
IR CTV EQD2 D98%	
Median	62.8
Range	60.1–65.5
Bladder EQD2 (D2cc)	
Median	81.1
Mean	80.86
Range	65.47–108.3
Rectum EQD2 (D2cc)	
Median	62.2
Mean	62.49
Range	46.88–75.67
Sigmoid EQD2 (D2cc)	
Median	58.62
Mean	57.65
Range	43.2-74.55
Small bowel EQD2 (D2cc)	
Median	67.47
Mean	66.79
Range	50.44–88.31

overall survival (OS). For the descriptive statistics of the data, the mean, median, minimum, maximum, and ratio were used. The Kaplan-Meier method was used to estimate local control, regional control, distant control, and OS. The log-rank test was performed to examine the effects of clinical variables. Correlations between toxicity and clinical or treatment parameters were determined by using the chi-square test. Univariate and multivarite logistic regression analysis was used to evaluate the correlation between the sum of the doses and toxicity. A p value <0.05 was considered to indicate statistical significance. Statistical analysis was performed using IBM SPSS Statistics® Version 21 software (IBM Corp., Armonk, NY, USA).

Results

Between 02.2019 and 05.2023, 40 patients were treated with SBRT after pelvic irradiation. The median follow-up time was 16 months (7–44 months). The median age was 49 years (range 28–82 years). The median Karnofsky performance status (KPS) was 90 (between 70 and 90). The tumor characteristics are summarized in Table 2.

The maximum tumor diameter measured on MRI was a median of 49.8 mm (range 22–96 mm). The median HR CTV was 47 cc (8.3-168.2 cc). The dosimetric characteristics of the HR and IR CTVs and critical organs are summarized in Table 3. The cumulative maximum D2 cc doses were exceeded for the bladder in 1 patient and for the bowel in 3 patients. The doses for the rectum and sigmoid were within limits for all patients. Dose plots illustrating the dose summation for critical structures are provided in the supplementary materials. For EBRT and SBRT treatments, the total walk-in to walk-out times in to the treatment room per session was calculated as an average of 11.4 min (range 7.8–18.4 min) and 15.2 min (range 9.8–32.5 min), respectively.

The total treatment time was 44 days (between 35 and 50 days). Except for one patient who received pembrolizumab as systemic treatment for metastatic disease, concurrent weekly 40 mg/m^2 cisplatin chemotherapy with a median of 5 times [2–5] was administered to all patients.

There were 39 patients who achieved a complete response and one who achieved a partial response in the third month after treatment. This patient with residual disease underwent a salvage hysterectomy in the sixth month. There were two local recurrences and two isolated regional recurrences (Fig. 2a, b). Patients with local recurrence were treated with salvage hysterectomy. In one patient, recurrence was limited to the cervix, while in the other patient, there was no residual disease in the cervix but there were metastases to the ovaries. One of the patients with isolated regional recurrence received SBRT to the external iliac lymph node followed by adjuvant immunotherapy, while the other patient underwent CRT to the para-aortic region. Distant metastasis was the most common cause of treatment failure. The 1- year metastasis-free survival was 88% (Fig. 2c). Six patients developed distant metastases with locoregional control. The 1-year

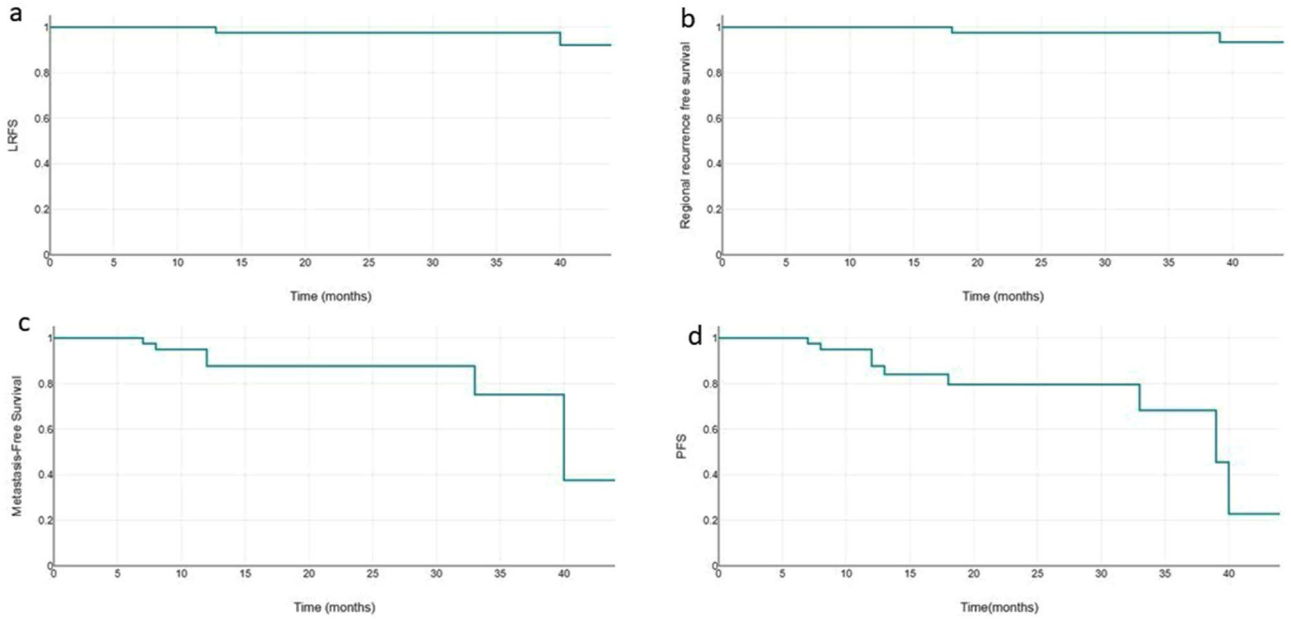

Fig. 2 Kaplan-Meier curves of (**a**) local control (**b**) regional control (**c**) distant control and (**d**) progression-free survival (PFS)

Table 4 Side effects

Side Effects	Grade	Number (%)
Gastrointestinal	Grade 0	37 (92.5)
	Grade I	1 (2.5)
	Grade II	1 (2.5)
	Grade III	1 (2.5)
Gynecological	Grade 0	28 (70)
	Grade I	11 (27.5)
	Grade II	1 (2.5)
	Grade III	0 (0)
Genitourinary	Grade 0	36 (90)
	Grade I	2 (5)
	Grade II	2 (5)
	Grade III	0 (0)

progression-free survival rate was 88% (Fig. 2d). One patient died due to disease progression.

The side effects are summarized in Table 4. During the follow-up period, grade 3 gastrointestinal side effects manifested as fecal incontinence in one patient, which subsequently resolved.

According to univariate logistic regression, there was a correlation between the sum of the bladder dose and genitourinary toxicity ($p=0.033$). However, there was no correlation between the rectum sum dose or sigmoid sum dose and gastrointestinal toxicity. No other dosimetric parameters were associated with any grade of toxicity. The FIGO stage, tumor diameter, HR volume, and KPS score were not correlated with any form of toxicity according to univariate analysis.

Discussion

In the present analysis, we reported the early results of SBRT as a dose escalation strategy in cervical cancer patients who refused or were ineligible for brachytherapy. This study represents the most extensive patient series conducted to date in the literature on this topic, exhibiting promising early-stage outcomes with a 92.5% local control rate and a notably low side effect profile in contrast to those of numerous other SBRT trials.

Studies investigating dose escalation with SBRT in cervical cancer patients in the literature are predominantly retrospective, with small sample sizes of 6–30 patients and relatively short follow-up durations of 3–40 months (Table 5). SBRT boost treatments are first administered to patients who are not eligible for brachytherapy or those who refuse brachytherapy [17–28]. There are also data on recurrent disease after definitive radiotherapy [25, 28]. In some of these studies, high toxicity rates of up to 44% have been reported, while in others, Grade 3≥adverse events have been reported as 0%. Due to the heterogeneity in patient selection criteria, radiation doses, and RT devices across all these studies, reaching a definitive conclusion regarding both local control rates and the profile of side effects is challenging.

An eminent contribution in this field is the prematurely terminated phase II study by Albuquerque, featuring an average follow-up of 19 months [22]. This study reported that 2-year oncological outcomes were lower than anticipated, with a cumulative grade 3 toxicity rate of 26.7% within the same period, which has been particularly associated with larger (planning target volume) PTV. Larger treatment volumes in SBRT applications are associated

Table 5 SBRT boost trials

Trial	Patient Number	Follow-up (month)	Treatment device	IGRT	Dose- fraction	Target Volume (cc)	Treatment Schedule	Grade 3 > toxicity (%)
Haas, 2012 [17]	6	14	Cyberknife	Fiducial tracking	19.5–20 Gy in 3–4	unavailable	EOD	0
Marnitz, 2013 [18]	11	14	Cyberknife	Fiducial tracking	30 Gy in 6	36.7	Every 72 h	0
Hsieh, 2013 [19]	25	3–40	Tomotherapy	MVCT	27 –16 Gy in 5–9	41.6	Every day or EOD	44
Kubicek, 2013 [20]	11	14	Cyberknife	Fiducial tracking	25 Gy in 5	9.16	EOD	9.9
Ito, 2019 [21]	6	7	Vero linac	CBCT (every ten minutes)	21–22.5 Gy in 3	unavailable	3 fraction in 5 days	0
Albuquerque, 2019 [22]	15	19	Cyberknife	Fiducial tracking	28 Gy in 4	81.7 ctv 138.8 ptv	At least 36 h apart	26.7
Morgenthaler, 2020 [23]	30	40	Cyberknife	Fiducial tracking	25–30 Gy in 5	unavailable	EOD	3
Dalvadi, 2020 [24]	25	25	Hexapod capable linac	not specified	24–30 Gy in 4–5	unavailable	EOD	4
Cheng, 2021 [25]	25	12	Varian linac	CBCT	10–25 Gy 2–5 gy	18.5 gtv	Unavailable	24
Facondo, 2021 [26]	9	16	Varian linac	CBCT	15–25 Gy in 3–5	63.9 ptv	Every 72 h	11
Hadi, 2022 [27]	10	9	Viewray MRL	Cine MRI	21 Gy in 4	35.2 ctv 43.5 ptv	EOD	0
Gultekin, 2022 [28]	21	28	Cyberknife	Fiducial tracking	25–30 Gy in 4–5	33 ctv 97 ptv	EOD	0
Present trial	40	16	Varian Edge	CBCT, SGRT	30 Gy in 5	47 ctv	EOD	2.5

MVCT: Megavolt Cone Beam CT CBCT: cone-beam CT SGRT: surface-guided radiotherapy EOD: Every other day MRL: magnetic resonance linac IGRT: Image Guided Radiation Therapy

with greater toxicity and lower local control rates [29, 30]. The larger target volumes observed in this study, compared to both our own study and others reported in the literature, may have contributed not only to higher toxicity rates but also to lower rates of local control. This finding points to a factor that needs to be considered in the selection of patients for SBRT.

The most significant factor distinguishing our study from previous SBRT trials is the evaluation of sum doses by merging planning CT modalities, contours, doses, and plans in Velocity software through deformable fusion. Thus, not only numerical calculations of doses but also volumetric and spatial characteristics have been determined, allowing SBRT plans to be better optimized based on information from the initial phase of treatment. Thus, better coverage in the tumor and more accurate doses in critical organs have been achieved.

Although this is not a comparative study with brachytherapy, based on our previous experience with brachytherapy, we would like to note a significant decrease in vaginal side effects. In our study, only 1 patient (2.5%) developed grade 2 vaginal atrophy and 2 patients (5%) developed grade 1 vaginal dryness. In the EMBRACE study, with an average follow-up of 15 months, the incidence of grade≥2 vaginal side effects was 29%, with vaginal atrophy being the most common within the first 6 months [31]. The addition of image guidance to brachytherapy applications reduces the incidence of severe vaginal side effects; however, the occurrence of Grade 1≥side effects in up to 90% of patients remains an inevitable consequence of brachytherapy applications [31]. Historically, the vagina has often been regarded as radioresistant and has received relatively little attention as a critical organ in the radiation therapy literature [32]. However, vaginal morbidity can significantly impact patients' quality of life. The lack of consensus regarding vaginal contouring, uncertainties in dose reporting methodologies, and the absence of standardized dose constraints may contribute to the observed high rates of vaginal morbidity. These factors emphasize the need for research on cervical cancer radiotherapy.

Inter-fractional changes are one of the main challenges in this anatomical region [33]. Although inter-fractional variations can be minimized by strict adherence to preparation protocols, some patients in our study needed to be removed from the treatment tables 2-3 times to ensure optimal tumor positioning and adequate filling of organs at risk [34]. This poses both challenges for patient

compliance and adds extra workload to the radiotherapy clinic. Online adaptation technologies can overcome the impact of inter-fractional differences and adapt treatments with real-time contouring and planning [14, 27]. In the study by Hadi and colleagues, although the reasons or objective criteria for adaptive planning were not explicitly stated, the fact that adaptive planning was performed in 100% of the fractions underscores the importance of daily anatomical variations and replanning in this region [27]. Additionally, the presence of spontaneous organ motion in this region emphasizes the importance of organ tracking in SBRT, especially for devices with relatively long treatment durations such as CyberKnife or MR linac, despite not being an issue in brachytherapy. The addition of tracking methods can further enhance the safety and efficacy of SBRT.

The main limitations of the trial are the small sample size and relatively short follow-up duration. This study included a heterogeneous patient group, including patients with locally advanced or metastatic disease and vaginal cuff recurrence after surgery. The standardized doses, standardized contouring, plan summation and compliance with strict dose constraints, and 3D volumetric (Image-Guided Radiation Therapy) IGRT including surface guidance procedures are the strengths of this study.

This article contributes to the current literature by showing low toxicity rates and reasonable locoregional control in a short follow-up period in cervical cancer patients.

Conclusion

While SBRT boost treatment may not be an alternative to standard brachytherapy for cervical cancer, it can be considered an option for some patients when brachytherapy is not possible. Further research is needed to establish the long-term oncological outcomes with toxicity data compared with those of standard brachytherapy.

Abbreviations

CRT	Chemoradiation
IMRT	Intensity-Modulated Radiation Therapy
SBRT	Stereotactic Body Radiotherapy
MRI	Magnetic Resonance Imaging
PET-CT	Positron Emission Tomography-Computed Tomography
SIB	Simultaneous Integrated Boost
LN	Lymph Node
EBRT	External Beam Radiotherapy
VMAT	Volumetric Modulated Arc Therapy
HR	High-risk
EQD2	Equivalent Uniform Dose in 2-Gy fractions
OAR	Organs at Risk
OS	Overall Survival
KPS	Karnofsky performance status
PTV	Planning Target Volume
IGRT	Image Guided Radiation Therapy

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-13017-8.

Supplementary Material 1

Author contributions

M.T.: Study design, data collection, analysis, and manuscript writing. R.R.: Study design and analysis. M.D.C.: Data collection and analysis. H.B.Ç.: Study design, manuscript revision, conceptualization.E.M.: statistic and analysis. N.K.: sturdy design and data collection.

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None.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Anadolu Medical Center affiliated with Johns Hopkins institutional ethics committee approved this study (number ASM-EK-21/162). The consent obtained from the participants was provided through an informed consent process.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med. 1999;340(15):1137–43. https://doi.org/10.1056/NEJM199904153401501.
2. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med. 1999;340(15):1144–53. https://doi.org/10.1056/NEJM199904153401502.
3. Eifel PJ, Winter K, Morris M, Levenback C, Grigsby PW, Cooper J et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: An update of Radiation Therapy Oncology Group Trial (RTOG) 90 – 01. Journal of Clinical Oncology. 2004;22(5):872–80. https://doi.org/10.1200/JCO.2004.07.197. PMID: 14990643.
4. Chino J, Annunziata CM, Beriwal S, Bradfield L, Erickson BA, Fields EC, et al. Radiation therapy for cervical cancer: executive summary of an astro clinical practice guideline. Practical Radiation Oncol. 2020;10(4):220–34. https://doi.org/10.1016/j.prro.2020.04.002. Epub 2020 May 18. PMID: 32473857; PMCID: PMC8802172.
5. NCCN Clinical Practice Guidelines in Oncology Cervical Cancer. Version 1.2023- January 6, 2023. [Online]. 2023. https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. (Accessed 2023, January 19.).
6. Chino J, Annunziata CM, Beriwal S, Bradfield L, Erickson BA, Fields EC, et al. The Astro Clinical Practice guidelines in cervical cancer: optimizing radiation therapy for improved outcomes. Gynecol Oncol. 2020;159(3):607–10. https://doi.org/10.1016/j.ygyno.2020.09.015.
7. Pötter R, Georg P, Dimopoulos JCA, Grimm M, Berger D, Nesvacil N, et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. Radiother Oncol. 2011;100(1):116–23. https://doi.org/10.1016/j.radonc.2011.07.012.

8. Charra-Brunaud C, Harter V, Delannes M, Haie-Meder C, Quetin P, Kerr C, et al. Impact of 3D image-based PDR brachytherapy on outcome of patients treated for cervix carcinoma in France: results of the French stic prospective study. Radiother Oncol. 2012;103(3):305–13. https://doi.org/10.1016/j.radonc.2012.04.007.
9. Gill BS, Lin JF, Krivak TC, Sukumvanich P, Laskey RA, Ross MS, et al. National cancer data base analysis of radiation therapy consolidation modality for cervical cancer: the impact of New Technological advancements. Int J Radiation Oncology*Biology*Physics. 2014;90(5):1083–90. https://doi.org/10.1016/j.ijrobp.2014.07.017.
10. Smith GL, Jiang J, Giordano SH, Meyer LA, Eifel PJ. Trends in the quality of treatment for patients with intact cervical cancer in the United States, 1999 through 2011. Int J Radiat Oncol Biol Phys. 2015;92(2):260–7. https://doi.org/10.1016/j.ijrobp.2015.01.037. PMID: 25968823; PMCID: PMC9807029.
11. Abel S, Lee S, Ludmir EB, Verma V. Principles and applications of stereotactic radiosurgery and stereotactic body radiation therapy. Hematol Oncol Clin N Am. 2019;33(6):977–87. https://doi.org/10.1016/j.hoc.2019.08.007.
12. Skowronek J. Current status of Brachytherapy in cancer treatment – short overview. J Contemp Brachytherapy. 2017;9(6):581–9. https://doi.org/10.5114/jcb.2017.72607.
13. Cilla S, Macchia G, Mattiucci G, Ianiro A, Romano C, Buwenge M, Azario L, Valentini V, Deodato F, Morganti AG. Optimized stereotactic volumetric modulated arc therapy as an alternative to brachytherapy for vaginal cuff boost. A dosimetric study. Med Dosim. 2020 Winter;45(4):352–8. Epub 2020 Jun 19. PMID: 32565068.
14. Dincer N, Ugurluer G, Mustafayev TZ, Serkizyan A, Aydin G, Güngör G, Yapici B, Atalar B, Özyar E. Dosimetric comparison of stereotactic MR-guided radiation therapy (SMART) and HDR brachytherapy boost in cervical cancer. Brachytherapy 2024 Jan-Feb;23(1):18–24. doi: 10.1016/j.brachy.2023.09.007. Epub 2023 Nov 23. PMID: 38000958.
15. Serviks kanserinde brakiterapi yerine stereotaktik beden radyoterapisi. Dozimetrik çalışma. TROD Virtuel Congress. 20–22 November 2020. Poster presentation. Nadir Küçük, Esra Küçükmorkoç, Emre Şanlı, Süleyman Çelebi, Hande Yaman, Doğu Canoğlu, Resad Rzazade, Menekşe Turna, Hale Başak Çağlar.
16. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31(5):1341-6. https://doi.org/10.1016/0360-3016(95)00060-C. PMID: 7713792.
17. Haas JA, Witten MR, Clancey O, Episcopia K, Accordino D, Chalas E. CyberKnife boost for patients with cervical cancer unable to undergo brachytherapy. Front Oncol. 2012;2. https://doi.org/10.3389/fonc.2012.00025.
18. Marnitz S, Köhler C, Budach V, Neumann O, Kluge A, Wlodarczyk W, Jahn U, Gebauer B, Kufeld M. Brachytherapy-emulating robotic radiosurgery in patients with cervical carcinoma. Radiat Oncol. 2013;8:109. https://doi.org/10.1186/1748-717X-8-109. PMID: 23638755; PMCID: PMC3695857.
19. Hsieh CH, Tien HJ, Hsiao SM, Wei MC, Wu WY, Sun HD, Wang LY, Hsieh YP, Chen YJ, Shueng PW. Stereotactic body radiation therapy via helical tomotherapy to replace brachytherapy for brachytherapy-unsuitable cervical cancer patients - a preliminary result. Onco Targets Ther. 2013;6:59–66. Epub 2013 Feb 4. PMID: 23403975; PMCID: PMC3569375.
20. Kubicek GJ, Xue J, Xu Q, Asbell SO, Hughes L, Kramer N, Youssef A, Chen Y, Aikens J, Saul H, Pahlajani N, LaCouture T. Stereotactic body radiotherapy as an alternative to brachytherapy in gynecologic cancer. Biomed Res Int. 2013;2013:898953. https://doi.org/10.1155/2013/898953. Epub 2013 Aug 13. PMID: 24000329; PMCID: PMC3755408.
21. Ito K, Kito S, Nakajima Y, Shimizuguchi T, Ogawa H, Nihei K et al. Determining the recommended dose of stereotactic body radiotherapy boost in patients with cervical cancer who are unsuitable for intracavitary brachytherapy: A phase I dose-escalation study. Japanese Journal of Clinical Oncology. 2019;49(9):856–61. https://doi.org/10.1093/jjco/hyz074. PMID: 31112278.
22. Albuquerque K, Tumati V, Lea J, Ahn C, Richardson D, Miller D, et al. A phase II trial of stereotactic ablative radiation therapy as a boost for locally advanced cervical cancer. Int J Radiation Oncology*Biology*Physics. 2020;106(3):464–71. https://doi.org/10.1016/j.ijrobp.2019.10.042.
23. Morgenthaler J, Köhler C, Budach V, Sehouli J, Stromberger C, Besserer A, et al. Long-term results of robotic radiosurgery for non brachytherapy patients with cervical cancer. Strahlenther Onkol. 2020;197(6):474–86. https://doi.org/10.1007/s00066-020-01685-x.
24. Dalwadi S, Echeverria A, Jhaveri P, Bui T, Waheed N, Tran D, Bonnen M, Ludwig M. Noninvasive stereotactic ablative boost in patients with locally advanced cervical cancer. Int J Gynecol Cancer. 2020;30(11):1684–8. https://doi.org/10.1136/ijgc-2019-001104. Epub 2020 Jul 6. PMID: 32636273.
25. Cheng HY, Liang JA, Hung YC, Yeh LS, Chang WC, Lin WC, Chen SW. Stereotactic body radiotherapy for pelvic boost in gynecological cancer patients with local recurrence or unsuitable for intracavitary brachytherapy. Taiwan J Obstet Gynecol. 2021;60(1):111–118. doi: 10.1016/j.tjog.2020.11.017. PMID: 33494982.
26. Facondo Giuseppe V, Gianluca M, Maria et al. Stereotactic body radiation therapy boost in patients with cervical cancer ineligible for Brachytherapy. Cancer Diagnosis & Prognosis. 2021;1(2):53–60. https://doi.org/10.21873/cdp.10008
27. Hadi I, Eze C, Schönecker S, von Bestenbostel R, Rogowski P, Nierer L, et al. MR-guided SBRT boost for patients with locally advanced or recurrent gynecological cancers ineligible for brachytherapy: feasibility and early clinical experience. Radiat Oncol. 2022;17(1). https://doi.org/10.1186/s13014-022-01981-z.
28. Gultekin M, Yilmaz MT, Yuce Sari S, Yildiz D, Ozyigit G, Yildiz F. Stereotactic body radiotherapy boost in patients with cervical cancer. J Obstet Gynecol. 2022;42(7):3033–40. Epub 2022 Jun 2. PMID: 35653802.
29. Redmond KJ, Gui C, Benedict S, Milano MT, Grimm J, Vargo JA, Soltys SG, Yorke E, Jackson A, El Naqa I, Marks LB, Xue J, Heron DE, Kleinberg LR. Tumor Control Probability of Radiosurgery and fractionated stereotactic radiosurgery for Brain metastases. Int J Radiat Oncol Biol Phys. 2021;110(1):53–67. Epub 2020 Dec 31. PMID: 33390244.
30. Milano MT, Grimm J, Niemierko A, Soltys SG, Moiseenko V, Redmond KJ, Yorke E, Sahgal A, Xue J, Mahadevan A, Muacevic A, Marks LB, Kleinberg LR. Single- and multifraction stereotactic radiosurgery Dose/Volume tolerances of the brain. Int J Radiat Oncol Biol Phys. 2021;110(1):68–86. Epub 2020 Sep 11. PMID: 32921513; PMCID: PMC9387178.
31. Kirchheiner K, Nout RA, Tanderup K, Lindegaard JC, Westerveld H, Haie-Meder C, Petrič P, Mahantshetty U, Dörr W, Pötter R. Manifestation pattern of early-late vaginal morbidity after definitive radiation (chemo)therapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: an analysis from the EMBRACE study. Int J Radiat Oncol Biol Phys. 2014;89(1):88–95. https://doi.org/10.1016/j.ijrobp.2014.01.032. PMID: 24725693.
32. De Felice F, Vicenzi L, Macchia G, Vavassori A, Perrucci E, Cerrotta A, Lancellotta V, Meregalli S, Draghini L, Augurio A, De Sanctis V. Vaginal toxicity management in patients with locally Advanced Cervical Cancer following Exclusive Chemoradiation-A Nationwide Survey on Knowledge and attitudes by the Italian Association of Radiotherapy and Clinical Oncology (AIRO) Gynecology Study Group. Med (Kaunas). 2023;59(2):385. https://doi.org/10.3390/medicina59020385. PMID: 36837584; PMCID: PMC9963963.
33. Panizza D, Faccenda V, Lucchini R, Daniotti MC, Trivellato S, Caricato P, et al. Intrafraction prostate motion management during dose-escalated linac-based stereotactic body radiation therapy. Front Oncol. 2022;12. https://doi.org/10.3389/fonc.2022.883725.
34. Maggio A, Gabriele D, Garibaldi E, Bresciani S, Delmastro E, Di Dia A, et al. Impact of a rectal and bladder preparation protocol on prostate cancer outcome in patients treated with external beam radiotherapy. Strahlenther Onkol. 2017;193(9):722–32. https://doi.org/10.1007/s00066-017-1163-4.

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